NON-FINAL REJECTION

Receipt is acknowledged of Applicants' Amendments and Remarks, filed 12/3/2009.

Claim 2 has been cancelled.

Claims 9, 15-17, 28, 36, 40, 43, and 45 have been amended and incorporate no new matter.

No new claims have been added.

Claims 4, 5, 7, 14, 23, 25-38, and 40-45 stand withdrawn as drawn to nonelected inventions and species.

Thus, claims 1, 3, 6, 8-13, 15-22, 24, 39, and 46 now represent all claims currently pending and under consideration.

STATUS OF THE CLAIMS

Applicant has requested clarification as to the status of claims 13, 39, and 46 (see Remarks dated 12/3/2009, p. 9). In the response dated 4/16/2009, Applicant elected the invention of Group I (claims 1-27, 39, and 46), and indicated that the elected species of polymeric carrier, Eudragit L 100-55; the elected species of active agent, brecanavir; and the presence of a surfactant, were encompassed by claims 1, 3, 6, 8-12, 15-22, and 24 (see Remarks dated 4/16/2009, p. 10). This indicated Applicant's view that the elected species did not read on claims 13, 39, and 46. In the Office Action dated 6/3/2009 (p. 6), the examiner indicated his interpretation that the elected species do encompass claims 13, 39, and 46, in addition to claims 1, 3, 6, 8-12, 15-22, and 24, such that claims 1, 3, 6, 8-13, 15-22, 24, 39, and 46 represented all claims pending and

under examination (as opposed to those pending but withdrawn as drawn to nonelected inventions and species). This interpretation is affirmed, and claims 1, 3, 6, 8-13, 15-22, 24, 39, and 46 remain currently pending and under examination.

INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statements (IDS) have been submitted.

WITHDRAWN REJECTIONS

Rejections under 35 USC §112

Applicant's amendments and arguments, see Remarks, pp. 9-10, filed 12/3/2009, with respect to the rejection of claims 1, 3, 6, 8-13, 15-22, 24, 39, and 46 as indefinite under 35 USC 112, second paragraph, have been fully considered and are persuasive. Therefore, this rejection has been withdrawn.

Applicant's arguments, see Remarks, p. 11, filed 12/3/2009, with respect to the rejection of claims 1, 3, 6, 8-13, 15-22, 24, 39, and 46 under 35 USC 112, first paragraph, for lack of an enabling disclosure commensurate with the scope of the claims, have been fully considered and are persuasive. Therefore, this rejection has been withdrawn.

Rejections under 35 USC §103

Applicant's arguments, see Remarks, p. 11, filed 12/3/2009, with respect to

the rejection of claims 1, 3, 6, 8-13, 15-22, 24, 39, and 46 under 35 USC 103(a) as obvious over Ignatious, Pendyala, Hale, and Verrick, as evidenced by CAS, Encyclopedia Britannica, and Mehta, have been fully considered and are persuasive. Therefore, this rejection has been withdrawn.

NEW REJECTIONS

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 1, 3, 6, 8-13, 15-22, 24, 39, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ignatious et al. (WO01/54667) in view of Law et al. (USPN 6,465,011), as evidenced by Evonik specification sheet for EUDRAGIT L-100-55 and Nazzal et al. (Drug Dev. Ind. Pharm. 28(1), 49–57 (2002)).

Ignatious discloses pharmaceutical compositions comprising an electrospun fiber of a pharmaceutically acceptable polymeric carrier integrated with a pharmaceutically acceptable active agent (p. 4, lines 9-11; claim 1). Specifically, Ignatious defines the term “integrated" to encompass a drug integrated with, admixed with, commingled with, or intermixed with the carrier, not coated on the surface of an electrospun fiber, which contains both the agent and the carrier together, preferably in a homogeneous manner (p. 4, lines 34-37). To provide a very large surface area, the disclosed electrospun fibers have diameters in the nanometer range (p. 5, lines 5-6), and the drug nanoparticles are

embedded homogenously in the polymeric nanofibers (p. 5, lines 29-30; claim 2), as recited by claims 1 and 3.

The electrospun dosage forms can have immediate, sustained, or pulsatile release characteristics (p. 5, lines 18-20), comprising an electrospun polymer in combination with an active agent, with which most benefit is achieved (i.e., enhanced bioavailability) employing active agents which are insoluble or sparingly soluble (p. 8, lines 15-16), as recited by claim 6. The compositions of Ignatious can taste-mask bitter or unpleasant-tasting drugs, regardless of their solubility (p. 9, lines 4-5), or a second taste-masking agent may be added (p. 14, line 14), as recited by claim 12.

Suitable drug substances include antiviral agents and lipid regulating agents (p. 8, lines 18-32); preferably, the active agent includes rosiglitazone (p. 9, line 25), carvedilol (p. 10, line 9), or (3S)-tetrahydrofuran-3-yl-(1S,2R)-3-[[(4-aminophenyl) sulfonyl](isobutyl) amino]-1-benzyl-2-(phosphonooxy)propylcarbamate (p. 10, lines 20-21), as recited by claims 16 and 17. In addition, Ignatious exemplifies an electrospun composition containing 25% (w/w) aspirin (Example 1), and 44% (w/w, prior to electrospinning) (S)-3-hydroxy-2-phenyl-N-(1-phenylpropyl)-4-quinolinecarboxamide (Example 14), as recited by claims 17 and 18.

The polymeric carriers are high-molecular weight (p. 10, lines 35-36); however, their particular physico-chemical characteristics dictate the design of the dosage form (immediate, sustained, or pulsatile release, etc.; p. 11, lines 2-6). Suitable polymeric carriers include hydroxypropylmethyl cellulose (HPMC) or water-insoluble polyacrylates and their derivatives, such as the EUDRAGIT family of polymers available from Rohm

Pharma (p. 11, lines 26-30; p. 13, lines 5-7). The genus of EUDRAGIT polymers includes EUDRAGIT L-100-55 (a.k.a. methacrylic acid copolymer type C; see Evonik specification sheet for EUDRAGIT L-100-55, attached), as recited by claims 8, 13 and 15.

The compositions of Ignatious may also comprise a surfactant, to include block copolymers of ethylene oxide and propylene oxide, lecithin, sodium dioctyl sulfo-succinate, sodium lauryl sulfate, sorbitan fatty acid esters, i.e., sorbitan monolaurate, monooleate, monopalmitate, monostearate, Triton X-200, polyethylene glycols, glyceryl monostearate, d-alpha-tocopheryl polyethylene glycol 1000 succinate, sucrose fatty acid esters, such as sucrose stearate, sucrose oleate, sucrose palmitate, sucrose laurate, and sucrose acetate butyrate, in amounts of about 10% w/w, preferably about 5% w/w or less (p. 15, line 23 to p. 16, line 2), as recited by claims 9 and 10.

The polymeric carrier or the surfactant may act as absorption enhancers, or an absorption enhancer may be added, to include chitosan, lecithin, lectins, sucrose fatty acid esters such as the ones derived from stearic acid, oleic acid, palmitic acid, lauric acid, and Vitamin E-TPGS (p. 16, lines 30-34), as recited by claim 11.

Further, Ignatious claims compositions intended for oral administration (claim 17), as recited by instant claim 19; comprising an active agent which demonstrates improved bioavailability (claim 18) and has a modified release profile (claims 22 and 23), as recited by instant claim 20. The electrospun fibers of Ignatious are encapsulated or compressed into a tablet (claim 19), as recited by instant claim 21; are further ground in size (claim 20), as recited by instant claim 22; and provide for

controlled release, sustained release, or pulsatile release of the active agent from the composition (claim 22), as recited by instant claim 24. This is an expected property of EUDRAGIT polyacrylates, which are taught as water insoluble polymers (p. 13, lines 5-8), which can provide controlled or pulsatile release profiles (p. 12, line 2-8).

While Ignatious does not explicitly teach that the polymeric carrier is amorphous, this is an inherent property of the disclosed EUDRAGIT family of polymers. Specifically, as evidenced by Nazzal et al. (2002), EUDRAGIT L 100-55 is an amorphous polymer that reveals no x-ray diffraction pattern (p. 54, col. 2).

Ignatious does not explicitly disclose active agents which are stable amorphous active agents, as recited by claim 1.

Law et al. disclose solid pharmaceutical formulations comprising a meta-stable, amorphous lipid-regulating agent dispersed in an amorphous polymer (abstract; claim 1). The lipid-regulating agents are fibrates, in particular fenofibrate (col. 1, lines 10-15), and suitable amorphous polymers include HPMC, as recited by claim 13, and the EUDRAGIT family of polyacrylates (col. 3, lines 21-25), as recited by claim 15. The compositions are formulated for oral administration (col. 3, lines 32-33), as recited by claim 19.

With respect to product-by-process claims 39 and 46, "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior

product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). Here, claims 39 and 46 depend from process claims which recite formulations "according to claim 1."

Although Ignatious and Law et al. disclose the genus of EUDRAGIT polyacrylate polymers available from Rohm Pharma as suitable polymeric carriers for these pharmaceutical compositions, neither reference discloses the applicant's elected species of EUDRAGIT L 100-55. However, Applicant contends that the priority document's disclosure of the genus of EUDRAGIT polyacrylate polymers is sufficient support within the meaning of 35 USC §112 to obtain benefit of the priority date (Remarks dated 12/3/2009, p. 15). Likewise, the cited references' disclosure of the genus of EUDRAGIT polyacrylate polymers is sufficient to support a case of *prima facie* obviousness over the elected species EUDRAGIT L 100-55.

The cited references do not disclose the elected species of active agent, (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl) amino]-2-hydroxy-1-{4-[(2-methyl-1,3-thiazol-4-yl)methoxy] benzyl}propylcarbamate (a.k.a. brecanavir, CAS 313682-08-5).

A skilled artisan would have been motivated to modify the compositions of Ignatious by employing the meta-stable, amorphous lipid-regulating agents disclosed by Law, because (1) Ignatious teaches that electrospun pharmaceutical dosage forms comprising drug nanoparticles homogenously embedded in a nanofiber polymeric carrier matrix have enhanced bioavailability, and can be formulated with various release profiles simply by selecting the appropriate polymer, without having to change the

process (p. 3, lines 32-37); and (2) Law et al. teach that delivery systems comprising an amorphous lipid-regulating agent dispersed throughout an amorphous polymer result in increased solubility and bioavailability, and improved dissolution rate of the active agent (col. 3, lines 12-14).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the electrospun pharmaceutical compositions comprising EUDRAGIT amorphous polymers and an active agent as taught by Ignatious, by using an amorphous active agent as taught by Law et al., to arrive at the claimed invention with a reasonable expectation of success, because both references disclose the combination of lipid-regulating agents with EUDRAGIT amorphous polymers in formulations having enhanced bioavailability and dissolution profiles. As recognized by MPEP §2144.06, "it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

RESPONSE TO ARGUMENTS

Evidentiary References

Applicant has requested clarification as to the evidentiary references cited in the statement of rejection under 35 USC §103(a) (Remarks dated 12/3/2009, p. 12). The Office Action dated 6/3/2009 rejected claims 1, 3, 6, 8-13, 15-22, 24, 39, and 46 as

obvious over Ignatious, Pendyala, Hale, and Verrick, as evidenced by CAS, Encyclopedia Britannica, and Mehta (see Remarks dated 12/3/2009, p. 12), which rejection is now withdrawn; and the current Office Action rejects claims 1, 3, 6, 8-13, 15-22, 24, 39, and 46 as obvious over Ignatious and Law et al., as evidenced by Evonik and Nazzal et al.

The references following the phrase "as evidenced by" are included in the rejection, but as evidentiary references only; that is, to establish on the record that certain limitations not explicitly taught by the substantive references are inherent therein. Rather than simply taking Official Notice, which is permissible only in limited circumstances, evidentiary references are cited as objective evidence in support of assertions made by the examiner. "It would not be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known. For example, assertions of technical facts in the areas of esoteric technology or specific knowledge of the prior art must always be supported by citation to some reference work recognized as standard in the pertinent art. *In re Ahlert*, 424 F.2d at 1091, 165 USPQ at 420-21." See MPEP §2144.03.

CONCLUSION

Claims 1, 3, 6, 8-13, 15-22, 24, 39, and 46 are rejected.

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to SARA E. CLARK whose telephone number is (571) 270-7672. The examiner can normally be reached on Mon - Thu, 7:30 am - 5:00 pm (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass, can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SARA E. CLARK/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612